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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JONES, Brian, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). ROUTLEDGE, Carol [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: SUMMERSELL, Richard, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

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(54) Title: COMPOSITION CONTAINING $5HT_{1A}$ and $5HT_{1D}$ ANTAGONISTS

(57) Abstract

The invention relates to novel combinations of $5HT_{1A}$ and $5HT_{1D}$ antagonists, pharmaceutical compositions containing them, and their use in therapy.

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COMPOSITION CONTAINING $5HT_{1A}$ and $5HT_{1D}$ ANTAGONISTS

The present invention relates to novel combinations of compounds, pharmaceutical compositions containing them, and their use in therapy.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders, including depression. WO94/03444 discloses a series of phenyl piperazine derivatives which are said to be $5HT_{1A}$ antagonists. These compounds are also said to be of use in the treatment of various CNS disorders, including depression.

It has now surprisingly been found that administration of a combination of a $5HT_{1D}$ antagonist and a $5HT_{1A}$ antagonist is likely to be much more effective in treating CNS disorders than administration of a single $5HT_{1D}$ or $5HT_{1A}$ antagonist.

In a first aspect the present invention therefore provides a pharmaceutical composition for the treatment or prevention of CNS disorders which comprises:

- a compound having $5HT_{1D}$ antagonist activity;
- a compound having $5HT_{1A}$ antagonist activity; and
- a pharmaceutically acceptable carrier.

It will be understood that compounds having $5HT_{1D}$ or $5HT_{1A}$ activity can usually be isolated in salt form and the invention extends to compositions in which the compounds are in salt form. Preferred salts are pharmaceutically acceptable salts, for example acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

The invention also extends to compositions in which the compounds are in stereoisomeric or tautomeric forms.

Preferred $5HT_{1D}$ antagonists include those disclosed in EPA 0 533 266/7/8, in particular N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide. Other preferred $5HT_{1D}$ antagonists include those compounds disclosed in WO 95/04729, WO 95/06044, WO 95/06644 and WO 95/06637.

Preferred $5HT_{1A}$ antagonists include those disclosed in WO 94/03444, in particular (+)-2,3,4,5,6,7-hexahydro-1-(4-(1-(1,2,3,6-tetrahydro-4-(2-methoxyphenyl)pyridyl))-2-phenyl-butyryl)-1H-azepine. Other preferred $5HT_{1A}$ antagonists are 1-(1H-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol, (*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin, N-tert-butyl 3-4-(2-methoxyphenyl) piperazin-1-yl-2-phenylpropanamide dihydrochloride and (N-(2-(4-(2-methoxyphenyl)-1-

piperazinyl)ethyl)-N-(2-pyridynyl)cyclohexanecarboxamide.

The compounds having $5HT_{1D}$ and $5HT_{1A}$ antagonist activity can be administered together or individually for the treatment of CNS disorders, that is to say either concurrently or non-concurrently.

As used herein, concurrently shall be understood to mean that the two agents are administered together or within 24 hours or less of each other, preferably within about 12 hours of each other, more preferably within about 1 hour of each other and most preferably within about 5 minutes of each other. Concurrent administration includes co-administration of separate dosage forms of the two agents or administration as a single dosage unit. Non-concurrently shall be taken to mean that the two agents are administered more than 24 hours apart.

In a further aspect of the present invention there is therefore provided a kit comprising in separate dosage forms a compound having $5HT_{1D}$ antagonist acitivity and a compound having $5HT_{1A}$ antagonist acitivity. In particular, such kits are of use in providing to patients when administration of separate doses of the two active ingredients is required. Such kits can also be provided where sequential administration of the $5HT_{1D}$ antagonist and $5HT_{1A}$ antagonist is required.

The invention also extends to pharmaceutical compositions comprising a compound having antagonist activity at both the $5HT_{1D}$ and $5HT_{1A}$ receptors, that is to say a single compound having dual activity, and a pharmaceutically acceptable carrier for the treatment or prevention of CNS disorders.

The compositions of the present invention are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

The compositions of the present invention may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore in a further aspect the present invention provides a pharmaceutical

composition which comprises a compound having $5HT_{1D}$ antagonist acitivity, a compound having $5HT_{1A}$ antagonist acitivity, and a pharmaceutically acceptable carrier for use in therapy.

In another aspect the invention provides a pharmaceutical composition which comprises a compound having $5HT_{1D}$ antagonist acitivity, a compound having $5HT_{1A}$ antagonist acitivity; and a pharmaceutically acceptable carrier in the manufacture of a medicament for the treatment of the aforementioned disorders.

In particular the invention provides a pharmaceutical composition which comprises a compound having $5HT_{1D}$ antagonist acitivity, a compound having $5HT_{1A}$ antagonist acitivity; and a pharmaceutically acceptable carrier for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Compositions of the invention can also be administered in combination with other medicaments, for example conventional antidepressants or anxiolytics.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a

compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

Preferred compounds of the invention can be prepared according to the following examples.

Example 1

N-[1-(2-Dimethylaminoethyl)indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

2'-Methyl-4'(5-methyl-11,2,4-oxadiazol-3-yl) [1,1'-biphenyl-4-carboxylic acid) (E.P.0533268-A1) (0.19g, 0.7mmol) was suspended in CH_2Cl_2 (15ml) and treated with oxalylchloride (0.065ml, 0.074mmol) followed by a drop of DMF. The mixture was stirred at room temperature for 1hr, then evaporated under reduced pressure to give a pale yellow solid. The solid was redissolved in dichloromethane (10ml) and added to a solution of 6-amino-1-(2-dimethylaminoethyl)-1H-indole (0.14g, 0.7mmol) in CH_2Cl_2 (10ml) containing Et_3N (0.19ml, 1.4mmol) under argon. After 19hr at room temperature, the reaction mixture was treated with water (20ml),extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil which was purified by flash column chromatography using CH_2Cl_2 as eluant. The title compound was isolated as a white solid. (90mg, 30%)

^1H NMR (250mHz, $CDCl_3$) δ : 8.40 (s, 1H) 8.20 (s, 1H) 7.99-7.90 (m, 4H), 7.53 (d, 1H), 7.39 (d, 2H), 7.30 (d, 1H), 7.12 (d, 1H), 7.08 (dd, 1H), 6.46 (d, 1H), 4.18 (t, 2H), 2.71-2.65 (m, 5H), 2.31 (s, 3H), 2.25 (s, 6H).

Example 2

(N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridynyl)cyclohexane-carboxamide

The title compound was prepared according to the procedure in EPA 0 512 755.

Evaluation of the effects of 5-$HT_{1D/1A}$ receptor antagonists by microdialysis in concious guinea pigs

The effects of 5-$HT_{1D/1A}$ receptor ligands on extracellular levels of 5-HT can be determined in vivo using the technique of microdialysis combined with high performance liquid chromatography and electrochemical detection (HPLC-ECD). Male Dunkin Hartley guinea pigs were anaesthetised with methoxyflurane and microdialysis probes were stereotaxically implanted into the frontal cortex (co-ordinates : 4.5 mm anterior, 2 mm lateral with reference to Bregma, lowered 3 mm from the skull surface). Microdialysis probes were secured to the skull surface using dental acrylic and the animals allowed a 24 hour recovery period. Probes were then perfused with artificial cerebrospinal fluid (aCSF) at a flow rate of 2 ul/min and samples collected every 20 min. Samples were then analysed for 5-HT and its metabolite 5-HIAA using HPLC-ECD. For data analysis 5-HT levels in the sample immediately prior to administration of drug or vehicle was taken as 100%, levels of 5-HT were then expressed as a % of this baseline level.

The following figures were obtained for 5-HT concentrations in the dialysates from frontal cortex expressed as a percentage of control, measured at the time of peak effect.

Compound A (5-HT_{1D} antagonist)
N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide:

0.3 mg/kg ip: -31 +/-12 (n=6)

Compound B (5-HT_{1A} antagonist)
(N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridynyl)cyclohexane-carboxamide:

1mg/kg ip: +20 +/-9 (n=5)

Compound A + Compound B

+405 +/-228 (n=5)

The results are shown graphically in Figure 1.

CLAIMS:

1. A pharmaceutical composition for the treatment or prevention of CNS disorders which comprises:

- a compound having $5HT_{1D}$ antagonist acitivity;
- a compound having $5HT_{1A}$ antagonist acitivity; and
- a pharmaceutically acceptable carrier.

2. A composition according to claim 1 in which the $5HT_{1D}$ antagonist is: N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

3. A composition according to claim 1 or 2 in which the $5HT_{1A}$ antagonist is (+)-2,3,4,5,6,7-hexahydro-1-(4-(1-(1,2,3,6-tetrahydro-4-(2-methoxyphenyl)pyridyl))-2-phenyl-butyryl)-1H-azepine,
1-(1H-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol,
(*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin,
N-tert-butyl 3-4-(2-methoxyphenyl) piperazin-1-yl-2-phenylpropanamide,
(N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridynyl)cyclohexane-carboxamide,
or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound having antagonist activity at both the $5HT_{1D}$ and $5HT_{1A}$ receptors and a pharmaceutically acceptable carrier.

5. A composition according to any one of claims 1 to 4 for use in the treatment or prevention of depression.

6. A kit comprising a dosage unit containing a $5HT_{1A}$ antagonist or a pharmaceutically acceptable salt thereof and a dosage unit containing a $5HT_{1D}$ antagonist or a pharmaceutically acceptable salt thereof.

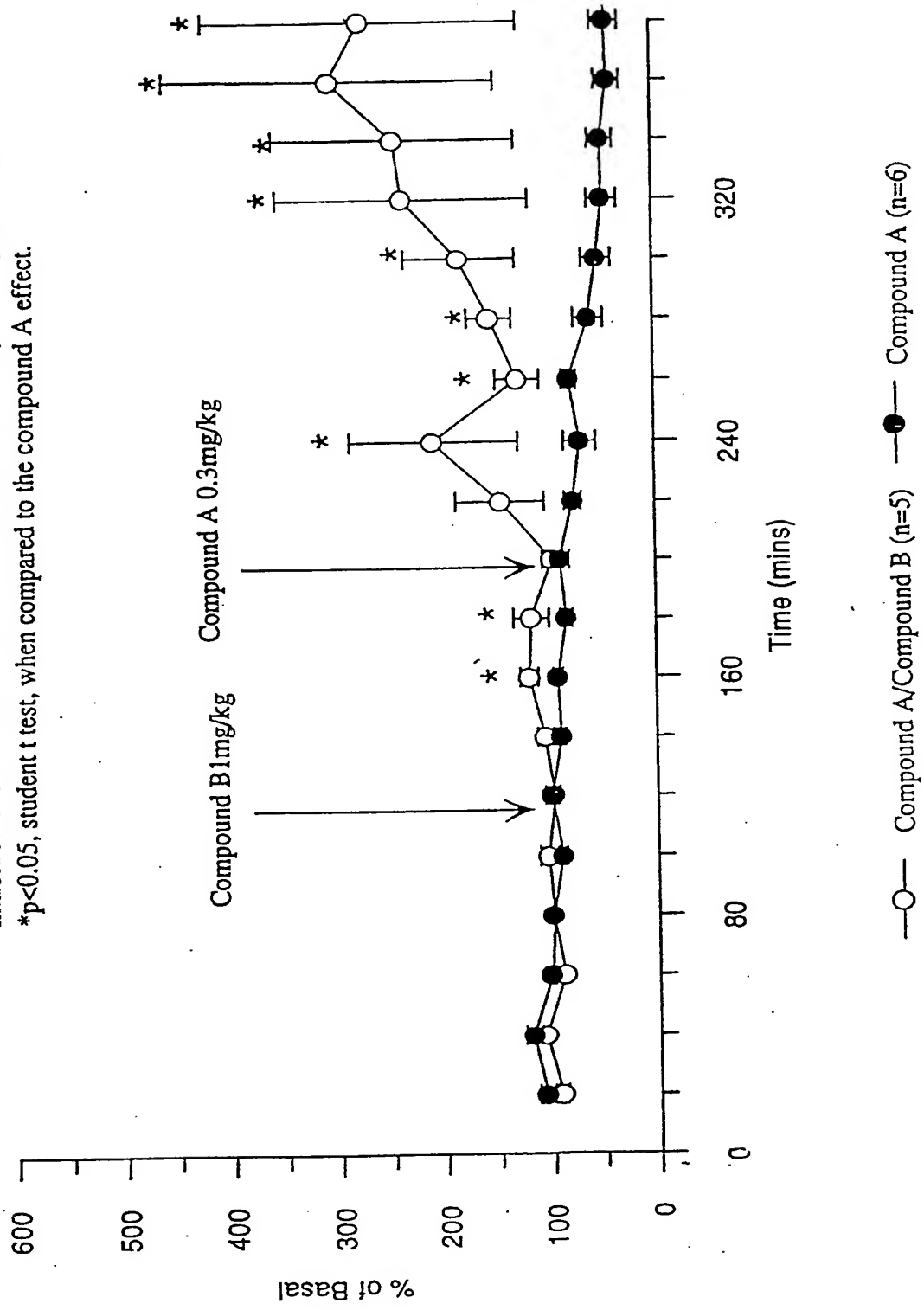

Fig 1

Effect of compound B (1 mg/kg ip) on the compound A (0.3 mg/kg ip) induced inhibition of 5HT levels in the frontal cortex of the freely moving guinea pig.
*p<0.05, student t test, when compared to the compound A effect.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 95/01916

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55 A61K31/495 //(A61K31/55,31:495),(A61K31/495,31:40, 31:13)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 533 267 (GLAXO GROUP LTD) 24 March 1993 cited in the application ---	
A	WO,A,94 03444 (WYETH) 17 February 1994 cited in the application -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

information on patent family members

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